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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,895	03/13/2007	Sabine Desset-Brethes	33316A	9283

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ONE HEALTH PLAZA 104/3
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EXAMINER	
KADAMBI, GEETA	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,895	DESSET-BRETHES ET AL.	
	Examiner	Art Unit	
	GEETA KADAMBI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending.

Claim Objections

1. Claims 15, 16 and 18 are objected to because of the following informalities: Claim 15 has “consists in” The applicant is requested to change that to “consisting of”. In claim 15 the “Hydroxypropylcelluloce” is mispelled and should be corrected to “Hydroxypropylcellulose” In claim 16 and 18 “pro cm^2” seems to be misspelled and the applicant may correct it to “per cm^2”.

Appropriate corrections are required.

Specification

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

3. The abstract of the disclosure is objected to use of legal phraseology, “comprising” (line 2, 4), “said” (line 4), “wherein” (line 6, 7) and “comprise” (line 7). Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear whether the terms in parenthesis in claim 1 are intended to further limit the subject matter of the claim or just to provide alternative terminology.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanizawa et al. (US 2004/0018235) and Dittmar et al. (US 6893662) in view of Dansereau et al. (US 5032406).**

'235 teaches using pitavastatin as a drug to treat hypercholesterolemia (instant claim 19) [0015]. '235 also discloses a controlled release pharmaceutical composition of pitavastatin [0015] using sustained release component, hydroxypropylmethyl cellulose [0017] (instant claim 8), polyvinyl derivative such as polyvinylpyrrolidone [0020] (instant claim 7), alkylene oxide polymers such as polyethylene glycol [0021] (instant claim 15). '235 teaches that amount of pitavastatin ranges from 0.01 to 60 mass % which reads on the instant claims 2 and 3 [0051]. In example 1 table 2 [0067] of '235 they teach the amount of pitavastatin to be 12 mg which is in the range of 1-32 mg claimed in instant claim 4. '235 in table 2 [0067] teaches that 24.00 mg of hydroxypropylmethyl cellulose is present in total weight of 256 mg of the formulation that equals to 9.3% of the

weight percent and reads on instant claim 9. In table 12 the percentage of magnesium alumino metasilicate (0.9 mg) of the total weight of 65 mg of the core tablet weight (1.3%) is within the range of 1-15% of the core component and reads on the instant claim 14. '235 in the same example teaches two different matrix formers in the form of low-substituted hydroxypropylcellulose and hydroxypropylmethyl cellulose which inherently have different viscosities and read on the instant claim 6.

'235 teaches use of a stabilizer magnesium alumino metasilicate and talc as claimed in instant claims 12, 13, 15 in table 2 and show that they about 7% of the magnesium alumino metasilicate of the total composition which reads on the instant claim 15. Pitavastatin-controlled release tablet can be produced by adding hydroxypropylmethyl cellulose, talc and titanium dioxide (table 15) [0139]. In para 0017, '235 teaches that pitavastatin release can be regulated by adding sustained release components, such as diluents (eg; hydroxypropylmethyl cellulose, polyvinylpyrrolidone), lubricants such as talc, coating agents methacrylate copolymers and alkylene oxide polymers such as polyethylene glycol. It would be obvious to one skilled in the art to make permutations and combination to achieve an optimal sustained release formulation by combining known components such as hydroxypropylmethyl cellulose, talc, polyethylene glycol and titanium dioxide as taught by various examples of '235. Non functional coat consists of PEG, titanium dioxide, talc and hydroxypropylmethyl cellulose in the instant claim and '235 teaches all these components as suitable coating components.

'235 teaches more than one type of matrix former component in table 5 [0090] and 7 [0100], these compounds are distinct and, absent evidence to the contrary, have different viscosities (instant claims 10 and 11). '235 teaches the composition to be made up of (A) and (B) components [0012]. (A) component is released in the stomach at pH 3.0 and the (B) component is enteric coated which is released in the duodenum [0012]. '235 further teaches the controlled release pharmaceutical composition of the present invention is preferably in the drug form of peroral preparation such as tablets, granules, or capsules. Examples of tablets include uncoated tablets, chewable tablets, film-coated tablets (equivalent to non-functional film coat), sugar-coated tablets, nucleated core-shell tablets, and multiple-layer tablets. Examples of capsules include hard capsules and soft capsules [0050]. The limitations of instant claim 1 of having an inner phase of the core, outer phase of the core can be explained by the examples in [0064] wherein they are mixing two types of tablet formation. In example (8) [0062] they explain the formation of a multiple layer tablet having a enteric composition (B) and a layer of the composition (A), which forms the core for example (10) [0064], hence the core of the tablet has two layers one outer and one inner. '235 also teaches that cholesterol is synthesized in the body during the period from midnight to morning [0002]. Although pitavastatin and salts and esters thereof are also known to exert high activity and have high safety, an excessively high blood level thereof is not preferred, from the viewpoint of prevention against the side effects [0003]. '235 teach that an

appropriate blood level of pitavastatin should be maintained for a long period of time [0005]. '235 teaches that pitavastatin exhibits high absorption in the large intestine as well as in the duodenum [0014]. One characteristic of pitavastatin, which serves an active ingredient of the controlled release pharmaceutical composition in the present invention, is high absorption thereof in the duodenum (see Table 1). Thus, the practical portion of pitavastatin released from the composition (A) in the stomach is considered to be absorbed in the duodenum. In contrast, the enteric composition (B) releases pitavastatin after passing through the near area of the duodenum. Thus, pitavastatin released from the composition (B) is firstly absorbed in the small intestine. The percentage of pitavastatin absorption in the small intestine is about one-third that in the duodenum (see Table 1). Therefore, even if pitavastatin is rapidly released in the small intestine, the abrupt absorption of pitavastatin does not occur. Furthermore, pitavastatin requires a relatively long period of time for the passage thereof through these organs. Thus, pitavastatin is slowly absorbed in sites; i.e., from the small intestine to the large intestine, over a relatively long time. Therefore, the controlled release pharmaceutical composition of the present invention can maintain a desirable blood level of pitavastatin [0013].

‘235 does not teach that the inner core has a matrix and the outer core does not have the matrix, non film layer below the enteric coating and specific coating concentrations.

'662 teaches an inner coating and an outer coating as enteric coating (col 2, ln 33-48). ‘662 also teaches the outer coating comprises of Eudragit ® L30 D-

55, an anionic copolymer derived from methacrylic acid and ethyl acrylate (col 6, ln 26-27), polyethylene glycol as a plasticizer, to enhance elasticity of the coating (col 6, ln 49-51), inert solids such as talc and titanium dioxide to facilitate the coating process (col 6, ln 64-67) (instant claim 17). This renders instant claim 17 obvious because the prior art teaches the same components as the instant claim. '662 teaches the need of two layers of coating by stating that for oral administration it minimizes the impact or negative effects of coating fractures, especially for larger or heavier dosage forms (col 2, ln 3-7). '662 also teaches in example 1 in col 9, ln 26-27 that the outer coating is sprayed on to tablets to achieve of 4.1 mg/cm^2 dried coating. '662 further teaches that the total coating thickness of the inner and outer coating layers combined is from about 5 mg/cm^2 to about 40 mg/cm^2. This renders the instant claims 16 and 18 obvious. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical (MPEP 2144.05). In the instant claims the combined weight falls between the prior art range and one ordinary skill in the art would be well aware of optimizing the range of coating of inner and outer coating.

'662 does not teach the use of matrix for the inner core and not for the outer core containing drug.

'406 teaches that the dosage form determines how rapidly the active ingredient is released. In turn, rate of release of active ingredient influences its blood plasma concentration (col 1, ln 16-19). '406 also teaches that typical

delayed release tablets dosage form uses enteric coated polymer systems to coat the tablet or capsule (col 1, ln 38-41). In contrast to delayed release tablets, sustained release tablets extend the duration of drug level in the body (col 1, ln 49-51). Typical sustained release formulations are coated tablets containing an active ingredient in a polymeric matrix (col 1, ln 53-55). Some dosage forms are designed to release portions of the active ingredient at different places in the gastrointestinal tract (col 1, ln 56-58). '406 teaches a dual action tablet (col 2, ln 23). '406 teaches that outer tablet contains first dose of active ingredient dispersed in a hydrophilic polymer matrix and the inner tablet contains a second dose of active ingredient (col 2, ln 23-29) and specifically teaches that hydroxypropylmethyl cellulose (col 4, ln 40) is a pH independent matrix (instant claim 5). This is the opposite of the instant claim 1. However, they do mention that dual action tablet can be contrasted with repeat action tablets which give an immediate dose followed by a sustained dose (col 2, ln 37-39). A person of ordinary skill in the art would be motivated to benefit from making the outer core as a delayed release layer and the inner core that contains the matrix to be the sustained release layer. '406 further teaches that rapid release of the active ingredient leads to higher elevation of concentration in plasma. However, the more quickly the active ingredient is eliminated from the organism's system, the more frequently must the active ingredient be administered to maintain the minimum effective concentration (col 1, ln 23-29). In the instant application the outer layer of the drug does not contain the matrix but is coated with an enteric coating so it would behave in similar manner as a delayed release layer. Delayed

release layer compositions offer advantages such as reduce dosing regimen, reducing side effects and targeting that portion of the alimentary canal in which the active ingredient will be released (col 1, ln 45-48). '406 further teaches sustained release formulations that contain a polymer matrix with active ingredient and reduce side effects, reduce drug accumulation with chronic dosing and reduce fluctuations in drug level (col 1, ln 53- 63) and extend the duration of drug level in the body (col 1, ln 50).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of the '235, '662 and '406 because '235 teaches all the components of the pharmaceutical composition that is taught by instant application such as a multilayer tablets as in example (8)- (10)[0061-0064], an inner core and outer core tablet as in a nucleated tablet product obtained by coating core tablets of a tablet product of (8) and/or (9) with the composition (A) for forming an outer layer [0064]. '662 teaches the need for two layers of coating for prevention of fracture and the range of thickness of the coatings. It would be obvious to make a non functional coat as claimed in instant claim 15 as taught by '235 or an enteric coat (consisting of methacrylic copolymer, talc and PEG) as claimed in instant claim 17 as taught by '662 to control the release of pitavastatin. '662 describes the benefit of having two layers such as inner coating layer (non-functional layer) and outer coating layer as enteric coating layer for minimizing the effects of coating fractures. '662 further describes that coating fractures may cause unreliable and inconsistent delivery or release or premature rupture or release of the therapeutic agent to the desired

region of the gastrointestinal tract (col 1, ln 62-66). ‘406 teaches the dual action tablet that is a combination of delayed release layer and a sustained release layer to maintain the level of active ingredient to a targeted site in the alimentary canal and the sustained release layer to extend the duration of drug level in the body. Since the synthesis of cholesterol is made for a long duration of time during midnight and morning, a tablet composition needs to meet this need. The combined references provide this need by enteric coated delayed release layer that would be absorbed in the duodenum and small intestine as taught by ‘235, ‘662 and ‘406 and the sustained release layer that contains the matrix would be absorbed in the large intestine. This also satisfies the absorption profile of pitavastatin as taught by '235 that pitavastatin requires a relatively long period of time for the passage thereof through the organs. Thus, pitavastatin is slowly absorbed in sites; i.e., from the small intestine to the large intestine, over a relatively long time [0013]. It would be obvious from the cited prior art to have a core with an inner phase which contains active ingredient with matrix and an outer phase which contains an active ingredient without matrix and coat with a non functional coat and then with an enteric coat enclosing the inner and outer core that as taught by ‘662 (instant claim 1). Each component is taught by the prior art to be useful for the same purpose, to optimize the release of pitavastatin in a sustained or controlled manner by coating the tablet. The idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).*

One would be motivated to make this combination of the said references to benefit from making a dual action delayed release and a sustained release drug composition for treating hypercholesterolemia with dual coating to prevent premature fracture of the tablet. Given the state of the art as evidenced by the teachings of the cited references and there would have been a reasonable expectation of success in combining the teachings of the cited references to obtain a pharmaceutical composition that has fewer side effects and reduces fluctuation in drug level in the body.

Conclusion

All claims are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GEETA KADAMBI whose telephone number is (571)270-5234. The examiner can normally be reached on 8 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GEETA KADAMBI
Examiner
Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614